

VIRUS, PREVIOUS INFECTIONS

#109R3

Activated: 10/1/64  
Renewed: 10/1/65  
Renewed: 10/1/66

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

633 THIRD AVENUE  
NEW YORK, N. Y. 10017

COMMITTEE:

Dr. Reimann, Chm.  
Dr. Sommers  
Dr. Jacobson

Application For Research Grant

Date: July 20, 1967

1. Name of Investigator(s): (include Title and Degrees)

Frederik B. Bang, M.D., Professor of Pathobiology

2. Institution &

Address:

The Johns Hopkins University School of Hygiene and Public Health  
615 North Wolfe Street, Baltimore, Maryland - 21205

3. Short Title of Project:

Pathogenesis of virus infections of respiratory mucosae

4. Proposed Starting Date:

To be continuous with present grant

5. Anticipated Duration of this Specific Study:

Three years

6. Brief Description of Objectives or Specific Aims:

- 1) Continue to study the effects of drugs and of internal and external environmental factors on susceptibility to viral infections, with emphasis on the initiation of infection.
- 2) Initiate a sequential study of regeneration and re-organization of mucosal cells following acute desquamation; for this study, nuclei will be labelled with tritiated thymidine, a method used extensively in studies of intestinal mucosae.
- 3) Study the effects of avitaminosis A on the susceptibility of chickens to the viruses of Newcastle disease and laryngotracheitis; we have found in preliminary studies that avitaminosis A (known to affect mucous epithelia) shows the first apparent effects histologically on the inner surface of the scroll of the maxillary concha, an area which we have found eminently vulnerable to virus infection.
- 4) With the collaboration of Dr. Donald F. Proctor, we propose to determine the effects of acute upper respiratory infections on the rate of nasal mucus clearance before, during, and after the acute clinical phase of infection; this will be a study on human volunteers, using a method which has proved reliable in a recent study which involved several hundred tests.

(Items 1, 3, and 4 will extend studies which have been primarily supported by the Council for Tobacco Research, and which have been published or are in press, as noted under item 12 below)

7. Give a Brief Statement of your Working Hypothesis:

Items 7, 11, 12 are on a separate attached page

1003546684

8. Details of Experimental Design and Procedures: (Attach Separate Pages)

1: Drugs are administered to chicks intramuscularly or locally; NDV is inoculated intranasally. Chicks are killed at intervals, the maxillary conchae excised, extensively washed, scraped, and the cells trypsinized; the number of infected cells is then determined by plaque techniques. 2: Tritiated thymine labelling will be done in pulses, and the progress and persistence of labelled cells determined at successive time intervals. 3: Chickens fed for 3 weeks after hatching on a commercial vitamin A-deprived diet will be inoculated with the two viruses and the spread of virus in the respiratory tract will be followed by titrations and by histology. 4: The rate of mucociliary clearance of the upper respiratory tracts of human volunteers will be recorded before, during, and after spontaneous acute upper tract infection. This is done by injecting a chemically inert tracer dye (Direct Sky Blue, Wyeth) onto a particular site on the anterior mucociliated part of the nasal fossa and timing its appearance in the nasopharynx, a method pre-tested for accuracy by running it simultaneously with a radioactive tracer in a series of volunteers.

(The numbers above are consistent with those of the experimental objectives given in Item 6)

9. Physical Facilities Available (Where Other than Administering Organization Indicate Geographical Location)

Fully equipped virus and histological laboratories.

10. Additional Requirements:

1) A full time histological technical trainee for routine histological sectioning; the present technical assistant, Mr. Raoul Spicker, to train this apprentice and to devote most of his own efforts toward autoradiography.

2) Half-time support for an additional animal man, to cover the increased use of animals requiring reliable supervision.

11. Biographical sketches of all principal and professional personnel (append)

(appended)

12. List of publications: (Five most recent as pertinent) (append)

(appended)

1003546685

## 7. Working hypothesis

1) Alterations in the mucous-ciliated epithelium which are induced by changes in the external and/or internal environment of the host will affect viral entry into mucosal cells.

2) The progress of infection from cell to cell, and the recovery of the mucous-ciliated epithelium following infection, are affected by mucous secretion. Avitaminosis A, known to induce conversion of mucous epithelium to squamous epithelium, should alter the progress of infection, particularly myxovirus infection

## 11. Biographical sketches

Frederik B. Bang, M.D., - b. November 5, 1916 in Philadelphia Pennsylvania. A.B. Johns Hopkins University 1935; M.D. Johns Hopkins School of Medicine 1939. Associate Professor of Medicine, Johns Hopkins School of Medicine 1949-1953; Professor of Pathobiology, Johns Hopkins School of Hygiene and Public Health 1953-1967. Special interests: virus pathogenesis; invertebrate immunology.

Betsy G. Bang, A.B., - b. July 9, 1912 in Lancaster, South Carolina. A.B. George Washington University 1933; Certification in Art as Applied to Medicine, Johns Hopkins School of Medicine 1937. Illustrator in Comparative Anatomy, American Museum Natural History 1937 - 1940; Research Associate in Pathobiology, Johns Hopkins School of Hygiene and Public Health 1962-1967. Specific interest: comparative functional anatomy of the upper respiratory tract.

Prantika Som, D.V.M., - b. August 31, 1942, Silchar, India. Inter-Science, Lady Bradbourne College, University of Calcutta 1960; B.V.Sc. and A.H., and D.V.M. Bengal Veterinary College, University of Calcutta 1965. Candidate for Sc.D. degree in Department of Pathobiology, Johns Hopkins University School of Hygiene and Public Health.

## 12. Recent pertinent publications

(1) Bang, F. B., and Foard, M.: Interaction of respiratory epithelium of the chick and Newcastle disease virus. Amer. J. Hygiene 1964 79:260

(2) Huang, J., and Bang, F.B.: The susceptibility of chick embryo skin organ cultures to influenza virus following excess vitamin A J. Exp. Med. 1964 120:129-148

(3) Bang, F. B., Bang, B. G., and Foard, M.: Responses of upper respiratory mucosae to drugs and viral infections. Amer. Review of Resp. Dis. 1966 93:142-149

(4) Bang, B.G., and Bang, F.B.: Laryngotracheitis virus of chickens: a model for acute desquamating rhinitis. J. Exp. Med. 1967 125:409-428

(5) Bang, B.G., Mukherjee, A.L., and Bang, F.B.: Human nasal mucus flow rates. (In press: Johns Hopkins Medical Journal) (In press: simultaneous abstract in J. Amer. Med. Assoc.)

1003546686

## 13. Budget: (1st year)

3.

## A. Salaries (Personnel by names)

Professional		% time	Amount
Marie A. Foard	Research Asst. in Pathobiology	50%	\$3625.00
<b>TECHNICAL</b>			
Raoul Spicker	Histologist	50%	3000.00
To be named	Histological Trahee	100%	5000.00
Technical Henry Johnson	Animal Attendant	88%	3060.00
Juhan Labidas	Animal Attendant	50%	1500.00
Linda Endemann	Glassware Washer	100%	3645.00
Gwendolyn Fatcher	Secretary	12%	752.00
Sub-Total			\$20582.00

## B. Consumable Supplies (list by categories)

Animal Food	1000.00
Histological Material	1000.00
Publications	600.00
Sub-Total	<u>\$2600.00</u>

## C. Other Expenses (itemize)

Travel-Domestic-to attend clinics	800.00
Requisition Payroll-to cover temporary summer help, termination payroll and special services	500.00
Fringe Benefits-6%:salaries and wages	1265.00
Sub-Total	<u>\$2565.00</u>

## D. Permanent Equipment (itemize)

Animal cages	1000.00
--------------	---------

\$26747.00

## E. Overhead (15% of A + B + C)

	3862.00
Total	\$30609.00

## Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	\$21318.00	\$2600.00	\$2610.00	\$1000.00	\$3980.00	\$31508.00
Year 3	\$23045.00	\$2600.00	\$2713.00	\$1000.00	\$4254.00	\$33612.00

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature

Director of Project

Signature

Business Officer of the Institution

Telephone

Telephone

1003546687

# Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

Current

Title of Project	Source	Amount	Duration
Comparative Anatomy of the Vertebrate Nasal Organ	NSF #GB5315	\$12800.00	7/1/66- 6/30/69

Pending

None

This grant to B.G. Bang finances a study of the comparative functional anatomy of the nasal folia, and is the source of  $\frac{1}{2}$  of Mr. Spicker's salary.

1003546688